

REPORT DOCUMENTATION PAGE

AD-A233 209

1b. RESTRICTIVE MARKINGS

3. DISTRIBUTION/AVAILABILITY OF REPORT

Approved for public release;
distribution is unlimited

4. PERFORMING ORGANIZATION REPORT NUMBER(S)

NMR1 91-7

5. MONITORING ORGANIZATION REPORT NUMBER(S)

6a. NAME OF PERFORMING ORGANIZATION
Naval Medical Research
Institute6b. OFFICE SYMBOL
(if applicable)7a. NAME OF MONITORING ORGANIZATION
Naval Medical Command6c. ADDRESS (City, State, and ZIP Code)
8901 Wisconsin Avenue
Bethesda, MD 20889-50557b. ADDRESS (City, State, and ZIP Code)
Department of the Navy
Washington, DC 20372-51208a. NAME OF FUNDING/SPONSORING
ORGANIZATION Naval Medical
Research & Development Command8b. OFFICE SYMBOL
(if applicable)

9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER

8c. ADDRESS (City, State, and ZIP Code)
8901 Wisconsin Avenue
Bethesda, MD 20889-5044

10. SOURCE OF FUNDING NUMBERS

PROGRAM
ELEMENT NO.PROJECT
NO.TASK
NO.WORK UNIT
ACCESSION NO.

62233N

MM33C30.04

1002

DN247509

11. TITLE (Include Security Classification)

Propranolol fails to lower the increased blood pressure caused by cold air exposure

12. PERSONAL AUTHOR(S)

Reed HL, Kowalski KR, D'Alesandro MM, Robertson R, Lewis SB

13a. TYPE OF REPORT
journal article13b. TIME COVERED
FROM TO14. DATE OF REPORT (Year, Month, Day)
199115. PAGE COUNT
5

16. SUPPLEMENTARY NOTATION

Reprinted from : Aviation, Space, and Environmental Medicine 1991 Vol.62 pp. 111-115

17. COSATI CODES

FIELD GROUP SUB-GROUP

18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)

Mean arterial pressure, norepinephrine, cold exposure, propranolol

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT

☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS

21. ABSTRACT SECURITY CLASSIFICATION

Unclassified

22a. NAME OF RESPONSIBLE INDIVIDUAL
Phyllis Blum, Librarian22b. TELEPHONE (Include Area Code)
(301) 295-218822c. OFFICE SYMBOL
MRL/NMRI

Propranolol Fails to Lower the Increased Blood Pressure Caused by Cold Air Exposure

H. L. REED, M.D., K. R. KOWALSKI, M.S.,
M. M. D'ALESSANDRO, Ph.D., R. ROBERTSON, and
S. B. LEWIS, M.D.

REED HL, KOWALSKI KR, D'ALESSANDRO MM, ROBERTSON R, LEWIS SB. *Propranolol fails to lower the increased blood pressure caused by cold air exposure.* Aviat. Space Environ. Med. 1991; 62:111-5.

Cold air exposure stimulates a rise in mean arterial blood pressure (MAP) and plasma norepinephrine (NE). The specific contribution of the beta-adrenergic receptor to this pressor response is unknown. Therefore, we pretreated 12 normal men with placebo or a bradycardia-inducing amount of propranolol prior to exposing them to either 25°C or 4°C air. At 25°C, propranolol pretreatment lowered heart rate (HR) and MAP. When we compared changes in MAP after their respective 30-min exposure at 25°C and 4°C, the cold elevated MAP by 18.4 ± 1.5 mm Hg in subjects pretreated with propranolol compared with 13.0 ± 2.5 mm Hg in subjects pretreated with placebo. Fingertip skin temperature (T_{fs}) measured at 4°C, $9.5 \pm 0.8^\circ\text{C}$ in propranolol-pretreated subjects was lower than the $11.1 \pm 0.7^\circ\text{C}$ with that of placebo. Plasma NE increased equally during cold exposure with both placebo and propranolol pretreatment. We conclude that the beta receptor plays a minor role in generating the pressor response to cold air. Therefore, the effectiveness of acute administrations of propranolol for maintaining normotension in subjects exposed to cold environments may be attenuated.

PROPRANOLOL, a nonselective beta-adrenergic blocking agent, fails to lower blood pressure when individuals suffer from pheochromocytoma (6), overdose on cocaine (15), or perform isometric exercise (13). We hypothesize that increases in circulating norepinephrine (NE) and unopposed alpha-adrenergic receptor stimulation are the common link for this failure. If the elevation of plasma NE with exposure to cold reflects higher concentrations at tissue receptors contributing to the cold pressor response, then this NE excess

may override propranolol's usual ability to lower blood pressure through beta adrenergic blockade. Propranolol, widely used to prevent recurrent migraine headaches and myocardial infarction (6), is commonly prescribed as an anti-hypertensive agent (22). Environmental cold exposure may contribute to seasonal elevations in myocardial infarction (21), cerebral vascular accident (11), and hypertension (19). The pressor response to a brief cold water immersion of the hand (4) or foot (8) is inconsistently attenuated with propranolol. The effectiveness of acute beta blockade in blunting the pressor response to cold air in motionless, normotensive men is uncertain (9).

The purpose of this study was to determine the contribution of the beta adrenergic receptor to the pressor response from cold air in normal subjects. We compared acutely administered bradycardia inducing doses of propranolol with placebo to make this assessment.

METHODS

Twelve healthy men gave informed consent to the protocol approved by our Institutional Review Board. The men were of similar age (mean \pm S.E.), 27.9 ± 1.9 years, weight, 72.4 ± 2.0 kg, and percent body fat, $13.8 \pm 0.3\%$. Each subject was tested in a climate chamber with alternating exposures at 25°C (25.6 ± 0.2) and 4°C (4.2 ± 0.2) for a total of two exposures at each temperature. There was a minimum of 72 h between exposures. Air flow in the chamber was 2.5 m/s at 20-40% humidity (Airguide Humidity Detector Model 605, Chicago, IL).

Placebo and propranolol were dispensed in double blind fashion as capsules filled with either white wheat flour for placebo or with a propranolol tablet (Wyeth-Ayerst Laboratories, Philadelphia, PA). The initial propranolol dose was 80 mg sustained release, and the second dose was 80 mg standard release. Both placebo and propranolol were self administered, with the first dose taken 10 h prior to entry into the chamber. After can-

From the Department of Environmental Medicine, Naval Medical Research Institute, Bethesda, MD 20814-5055.

This manuscript was received for review in July 1990. The revised manuscript was accepted for publication in August 1990.

Address reprint requests to: H. Lester Reed, M.D., who is Head, Biochemistry Division, Mail Stop 11, Department of Environmental Medicine, Naval Medical Research Institute, Bethesda, MD 20814-5055.

nulation of the antecubital vein, each subject ingested the second dose of placebo or propranolol with 500 ml of water while seated in the staging room (25°C) for 30 min before entering the chamber. Subjects were randomly divided into two groups, each with a fixed sequence of alternating temperature and either placebo or propranolol administration. Half the subjects received placebo first, then propranolol, and the other half received the drug treatment in the reverse order. Temperature exposure was alternated for each administration of placebo or propranolol with all men exposed to control (25°C) temperature first. All subjects were tested in the post absorptive state and underwent all tests at the same time of day. This protocol facilitated chamber scheduling and drug washout periods. Clothing consisted of undershirt, socks, and shorts.

Physiological Data

Temperatures were recorded with thermocouples (Sensortek BAT 12, Clifton, NJ) from a site in the rectum more than 10 cm proximal to the anal sphincter (T_{re}) and on the distal pad of the middle finger (T_{fing}) using thermistors (Yellow Springs Instruments, Yellow Springs, OH). Fingertip capillary blood flow (LDF) was monitored on the distal pad of the index finger by a laser Doppler volumetric recorder (Medpacific Corporation, Seattle, WA). Temperature and LDF measurements were recorded (Techmar Labmaster, Solon, OH) and stored in a Zenith 248 computer (Glenview, IL). A single exponent model was fitted to the T_{fing} data for each individual. Estimates for T_{fing} at time 0 and 30 min of exposure were individually calculated and the mean of all subjects then reported. Blood pressure and heart rate (HR) were measured from the uncannulated arm with an automated instrument (Takeda Medical UA-751, Bristol, CT). Mean arterial pressure (MAP) was calculated as: pulse pressure/3 + diastolic. MAP, HR, and LDF were determined 30 min before entering the chamber (-30 min); 0, 1, 5, 10, 15, 20, 25, and 30 min in the chamber; and 30 min after returning to the staging room.

Blood Analysis

Venous blood samples were obtained following cannulation (-30 min), prior to entry into the chamber (0 min), after 15 and 30 min in the chamber, and 30 min after returning to the staging area (+60 min). Plasma

catecholamines from heparinized blood (14.3 USP units/ml) were analyzed by high pressure liquid chromatography methods previously reported (17). Propranolol does not interfere with catecholamine analysis using this technique (12). Heparinized whole blood hematocrit was measured after capillary tube centrifugation.

Statistical Analysis

Study subjects were randomized by complete blocks into repeated split plot in time groups for temperature and drug factors. When no significant difference was determined among groups of drug and temperature schedules ($p > 0.05$), the 12 subjects were considered as one group. Analysis of variance (ANOVA) in split plot design with two repeated measures and simple two way ANOVA for repeated measures were used as indicated. Analyses were performed using STATPAK 4.1 (Northwest Analytical Inc., Portland, OR) and SAS (SAS Institute, Cary, NC). The data are expressed as the mean \pm S.E. of the mean.

RESULTS

Finger and Rectal Temperatures and Blood Flow

T_{fing} with propranolol pretreatment tended to be lower than placebo before either the 4°C (24.8 ± 1.5 , $27.2 \pm 1.5^\circ\text{C}$) or 25°C (25.7 ± 1.4 , $28.4 \pm 1.4^\circ\text{C}$) exposure ($F_{(1,11)} = 5.69$, $p < 0.04$). Cold air exposure for 30 min lowered T_{fing} significantly for both treatments ($p < 0.0001$). With cold exposure, T_{fing} was lower with propranolol pretreatment ($9.5 \pm 0.8^\circ\text{C}$) compared with placebo pretreatment ($11.1 \pm 0.7^\circ\text{C}$) ($p < 0.008$). With both temperature treatments, T_{re} fell slightly over time without any significant effect of propranolol administration. Compared with 25°C, LDF in cold air fell after 1 min and was lower for this exposure ($F_{(1,23)} = 13.65$, $p < 0.002$) (Table I). No significant differences in LDF between propranolol and placebo pretreatments at either 25° or 4°C was detected.

Blood Pressure and Heart Rate

MAP measured upon arrival at the laboratory (-30 min) was lower with propranolol pretreatment compared to placebo before both the 4°C (85.9 ± 1.5 , 89.8 ± 2.1 mm Hg) and 25°C (83.2 ± 1.8 , 88.4 ± 2.6 mm Hg) treatments. After 30 min at 25°C, propranolol lowered MAP to 75.7 ± 2.4 mm Hg compared with placebo, 81.9

TABLE I. COMPARISON OF FINGERTIP SKIN BLOOD FLOW WITH EXPOSURE TO 25°C or 4°C AIR AND PRETREATMENT WITH PLACEBO OR PROPRANOLOL.

Time (min.)	In Chamber									
	-30	0	1	5	10	15	20	25	30	60
Placebo 25°C	228.3	114.1	145.0	152.5	160.0	144.1	194.1	140.8	115.8	125.0
	54.1	31.3	55.6	52.8	53.5	42.2	67.5	44.6	34.5	48.4
Placebo 4°C	278.3	116.6	44.1	28.3	27.5	35.8	40.8	46.6	54.1	90.0
	75.2	38.0	9.5	5.7	6.4	8.0	6.9	6.7	7.9	23.9
Propranolol 25°C	220.0	107.2	95.8	100.0	128.3	156.6	148.3	150.8	132.5	85.0
	77.0	42.6	38.5	40.8	46.5	53.4	43.5	48.3	43.3	32.8
Propranolol 4°C	137.5	84.1	31.6	22.5	20.0	30.8	39.1	49.1	53.3	95.0
	40.7	46.7	7.0	4.1	2.7	10.4	4.1	8.9	15.3	35.5

The first line is the ANOVA mean of 12 men with the SE of the mean in the second line; Doppler flow is measured in millivolts; temperature treatment $p < 0.002$.

± 2.2 mm Hg ($p < 0.03$). In contrast, MAP was similar after 30 min at 4°C in both treatment groups (propranolol, 94.2 ± 1.9 ; placebo, 94.9 ± 1.8 mm Hg). When we compared the difference between 25 and 4°C, the MAP tended to increase more for propranolol treatment than with placebo treatment ($F_{(1,11)} = 4.07$, $p = 0.068$) (Fig. 1). However, after 1 min in the climate chamber, the increase at 4°C compared to 25°C became significantly greater with propranolol pretreatment than with placebo ($F_{(1,11)} = 5.11$, $p < 0.05$). After 30 min of cold exposure, the percentage increase over the corresponding value at 25°C was $25.0 \pm 2.5\%$ with propranolol and $16.6 \pm 3.2\%$ with placebo pretreatment. This marked difference was caused primarily by lower MAP at 25°C with propranolol pretreatment compared with that of placebo at 25°C. Blood pressure is presented in Table II and shows near equal elevations in systolic and diastolic pressure with cold exposure. Basal HR (-30 min) was lower in subjects pretreated with propranolol when compared with subjects pretreated with placebo at both 25°C (59 ± 2 , 68 ± 5 min $^{-1}$) and 4°C (59 ± 2 , 66 ± 3 min $^{-1}$) ($F_{(1,11)} = 7.75$, $p < 0.02$). The HR after 30 min in both 25°C ($p < 0.00001$) and 4°C ($p < 0.00001$) environments was slower for propranolol (52 ± 2 , 55 ± 3 min $^{-1}$) compared with placebo (63 ± 2 , 64 ± 2 min $^{-1}$). There was no significant effect of temperature upon HR.

Plasma Norepinephrine and Epinephrine

Plasma venous NE was unchanged after 30 min at 25°C and after pretreatment with propranolol or placebo. Plasma NE increased after 30 min at 4°C from 2.23 ± 0.25 to 6.09 ± 0.60 (propranolol) and from 2.50 ± 0.28 to 5.96 ± 0.41 (placebo) nmol/L (Fig. 2). Epinephrine (EPI) values were unchanged during 25°C exposure (Fig. 3). However, pretreatment with propranolol prior to cold exposure significantly elevated EPI compared with placebo pretreatment (Fig. 3). Whole blood hematocrit increased after 30 min of cold exposure ($F_{(1,11)} = 26.18$, $p < 0.0004$) from 41.40 ± 0.81 to $43.56 \pm 0.87\%$ for placebo pretreatment and from 41.91 ± 0.59 to $44.08 \pm 0.94\%$ for propranolol pretreatment. Propranolol had no effect upon this increase ($p > 0.99$).

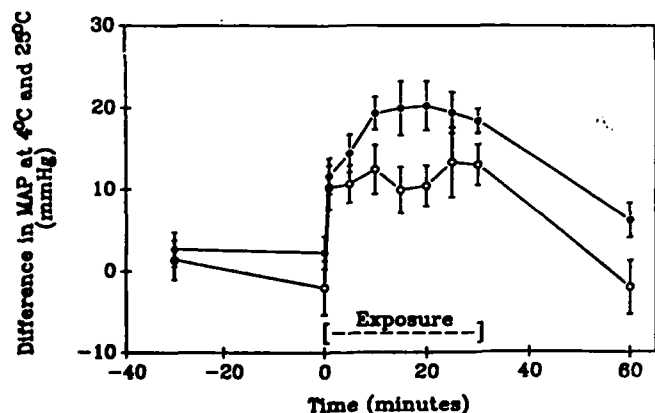


Fig. 1. The difference in mean arterial blood pressure (MAP) in mm Hg at 4°C and 25°C air after pretreatment with placebo (—○—) or propranolol (—●—). The dashed line indicates exposure period in the environmental chamber.

DISCUSSION

We and others report that when human subjects are exposed briefly to cold air, a characteristic series of thermoregulatory and cardiovascular events are noted (14,16). These events include a fall in the oxygenation of brachial venous hemoglobin (17), an increase of the viscosity of blood (10), a near doubling of the oxygen uptake (1), an increase in mean arterial pressure (20), and a two-fold increase in plasma norepinephrine (7,14,16). We demonstrate in this study that cold air challenge has an acute pressor action that overcomes the normal blood pressure lowering influence of propranolol. We suggest that the pressor response of cold is mediated primarily by a mechanism other than the beta adrenergic component of the sympathetic nervous system.

Cold exposure enhances cutaneous vasoconstriction, shunts blood to the central circulation, and elevates systolic and diastolic blood pressure without an equivalent increase in cardiac output (5,16). In our study, the rapid fall in fingertip skin blood flow (Table I) with cold exposure parallels the rise in MAP (Fig. 1). This finding agrees with a cold-induced shift in blood volume from the cutaneous to the central circulation (16). Heart rates are similar for each treatment group independent of temperature, and both systolic and diastolic pressure rise equally in response to cold (Table II). Therefore, MAP, in contrast to a rate \times pressure calculation, is a convenient and accurate way to compare cold responses with those found at room temperature (18). Comparisons of MAP at 4°C and 25°C show that MAP increases 25% for propranolol and only 16% for placebo. This 25% increase in MAP, while the propranolol-treated subjects are bradycardic, suggests that the beta receptor contributes only minimally to generating the cold pressor response in these normal men.

Dosing intervals similar to those used in our study have been shown to provide serum levels of propranolol associated with nonselective beta blockade (2,3,20). Slowing of the resting heart rate, as in our subjects, indicates physiologic myocardial beta-1 blockade; we thus presume beta-2 blockade (22). Because this acute dosing study involves nonsteady-state blood levels of the drug, all physiologic measurements are best compared with their paired drug and temperature counterparts to minimize the interaction of time. At 25°C, propranolol, compared with placebo, significantly lowers blood pressure and HR within 60 min after acute dosing and suggests that serum levels are adequate to achieve beta blockade. At 4°C, propranolol retains its effect of bradycardia. This similar chronotropic effect between temperatures suggests circulating and physiologic levels of propranolol at 4°C are comparable to those found at 25°C. However, at 4°C, propranolol no longer lowers blood pressure, implying an overriding intervention by cold not mediated by HR.

Peripheral venous plasma NE consistently increases with cold exposures (7,14,17). The nearly three-fold elevation in NE at 30 min of cold exposure that we describe is maintained after 30 min of rewarming. Cold-induced alpha-adrenergic receptor activation by NE, unopposed with propranolol blockade of the beta receptor, could produce the changes in MAP we observe.

PROPRANOLOL & COLD EXPOSURE—REED ET AL.

TABLE II. COMPARISON OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE (mm Hg) WITH EXPOSURE TO 25°C or 4°C AIR AND PRETREATMENT WITH PLACEBO OR PROPRANOLOL.

Time (min.)	In Chamber									
	-30	0	1	5	10	15	20	25	30	60
Placebo 25°C										
Systolic	124.5	113.2	116.2	111.5	114.8	113.3	113.6	114.1	112.0	116.0
	4.5	3.4	2.8	2.2	3.3	3.6	3.2	2.4	2.2	1.3
Diastolic	70.5	71.3	72.2	70.8	68.8	68.0	69.5	68.4	66.9	73.2
	2.6	3.8	2.4	2.2	2.5	2.0	2.7	2.8	2.7	2.7
Placebo 4°C										
Systolic	121.0	111.5	125.7	126.3	128.5	123.7	128.4	127.0	126.1	115.6
	2.8	2.6	3.9	3.1	3.2	3.2	2.8	4.0	2.5	2.7
Diastolic	74.3	69.1	82.9	80.0	80.5	77.6	78.4	81.9	79.4	72.8
	2.6	2.3	3.5	2.2	2.4	2.3	2.7	4.0	2.5	1.7
Propranolol 25°C										
Systolic	114.5	103.9	103.4	104.0	101.0	100.6	98.9	100.3	100.5	100.5
	2.1	1.6	2.0	1.6	2.8	2.4	3.3	2.3	2.6	1.6
Diastolic	67.5	67.5	66.0	66.1	61.8	62.6	63.4	63.0	63.3	63.3
	2.3	2.3	2.1	2.2	2.3	2.1	1.7	1.8	2.7	2.0
Propranolol 4°C										
Systolic	115.5	108.1	117.9	117.2	123.5	121.8	121.0	121.4	120.6	107.0
	1.4	1.9	2.5	2.1	2.5	2.5	1.9	3.3	2.7	2.8
Diastolic	71.2	67.7	76.2	78.5	79.3	81.9	83.0	81.6	81.0	69.4
	2.0	2.7	3.2	3.1	2.7	3.4	3.1	2.7	1.9	3.3

The first line is the ANOVA mean of 12 men with the SE of the mean in the second line; pressures are measured in mm Hg.

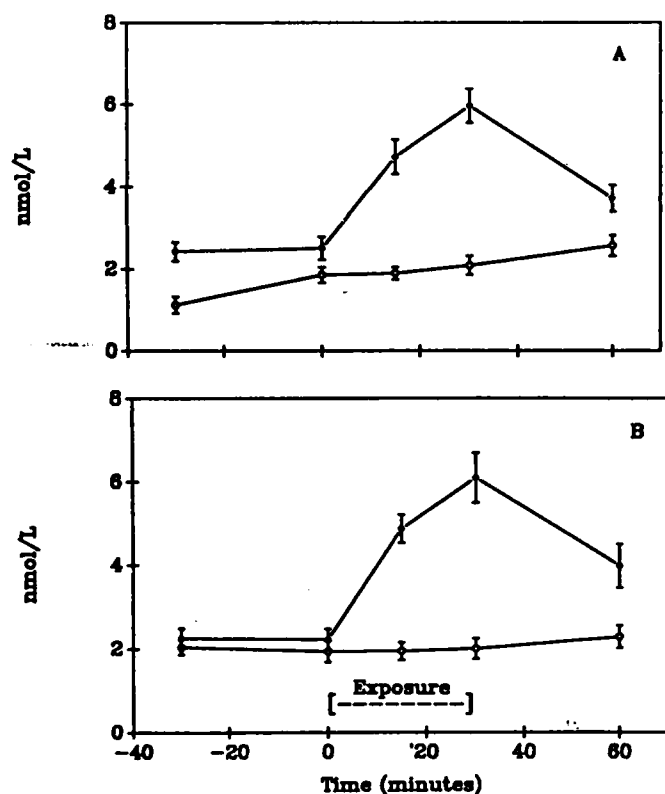


Fig. 2. Comparison of plasma norepinephrine levels (nmol/L) with exposure to 25°C (—○—) or 4°C (—●—) air after pretreatment with placebo (Graph A) or propranolol (Graph B). The dashed line indicates exposure period in the environmental chamber.

This finding is supported by reports that propranolol does not lower the MAP elevation associated with pheochromocytoma (6), cocaine overdose (15), and isometric exercise (13), conditions also associated with increased alpha-adrenergic stimulation. The acute use of

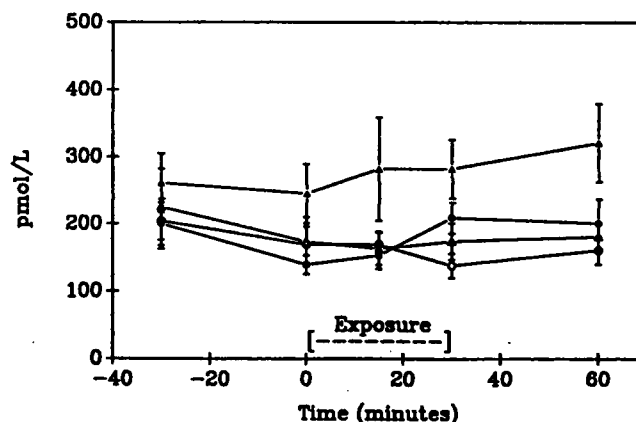


Fig. 3. Comparison of plasma epinephrine levels (pmol/L) with exposure to 25°C or 4°C air after pretreatment with placebo or propranolol (—○— 25°C, placebo; —●— 4°C, placebo; —△— 25°C, propranolol; —▲— 4°C, propranolol). The dashed line indicates exposure period in the environmental chamber.

propranolol in maintaining 24-h normotension may have reduced effectiveness in cold climates.

ACKNOWLEDGMENTS

The authors thank Dr. K. D. Burman for discussions about the protocol, Dr. J. D. Wallin for review of the manuscript, Dr. L. D. Homer and D. Armstrong for discussions and recommendations regarding statistical analysis, and P. J. Mullinix for manuscript preparation.

The opinions expressed herein are those of the authors and are not to be construed as reflecting the views of the Navy Department, the Naval Service at large, or the Department of Defense. Supported by Naval Medical Research and Development Command work unit number 62233N.MM33C30.004.1002.

REFERENCES

1. Bittel JHM. Heat debt as an index for cold adaptation in men. *J. Appl. Physiol.* 1987; 62:1627-34.

PROPRANOLOL & COLD EXPOSURE—REED ET AL.

2. Carruthers SG, Pacha WL, Aellig WH. Contrasts between pin-dolol and propranolol concentration-response relationships. *Br. J. Clin. Pharmacol.* 1985; 20:417-20.
3. Dey M, Brisson J, Davis G, *et al.* Relationship between plasma propranolol concentration and dose in young, healthy volunteers. *Biopharm. Drug Dispos.* 1986; 7:103-11.
4. Dikshit MB, Patrick JM. Beta-adrenoceptor blockade and cardiovascular response to the cold pressor test. *Indian J. Physiol. Pharmacol.* 1986; 30:1-10.
5. Epstein SE, Stampfer M, Beiser GD, Goldstein RE, Braunwald E. Effects of a reduction in environmental temperature on the circulatory response to exercise in man. *N. Engl. J. Med.* 1969; 280:7-11.
6. Frishman WH. β -adrenergic blockers. *Med. Clin. North Am.* 1980; 72:37-81.
7. Hiramatsu K, Yamada T, Katakura M. Acute effects of cold on blood pressure, renin-angiotensin aldosterone system, catecholamines and adrenal steroids in man. *Clin. Exp. Pharmacol. Physiol.* 1984; 11:171-9.
8. Houben H, Thien T, Wijnands G, Van'tLaar A. Effects of cold exposure on blood pressure, heart rate and forearm blood flow in normotensives during selective and non-selective β -adrenoceptor blockade. *Br. J. Clin. Pharmacol.* 1982; 14:867-70.
9. Juneau M, Johnstone M, Dempsey E, Waters DD. Exercise-induced myocardial ischemia in a cold environment: effect of antianginal medications. *Circulation* 1989; 79:1015-20.
10. Keatinge WR, Coleshaw SRK, Cotter F, Mattock M, Murphy M, Chelliah R. Increases in platelet and red cell counts, blood viscosity, and arterial pressure during mild surface cooling: factors in mortality from coronary and cerebral thrombosis in winter. *Br. Med. J.* 1984; 289:1405-8.
11. Keatinge WR, Coleshaw SRK, Holmes J. Changes in seasonal mortalities with improvement in home heating in England and Wales from 1964 to 1984. *Int. J. Biometeorol.* 1989; 33:71-6.
12. Koller M. Results for 74 substances tested for interference with determination of plasma catecholamines by "high-performance" liquid chromatography with electrochemical detection. *Clin. Chem.* 1988; 34:947-9.
13. O'Hare JA, Murnaghan DJ. Failure of anti-hypertensive drugs to control blood pressure rise with isometric exercise in hypertension. *Postgrad. Med. J.* 1981; 57:552-5.
14. O'Malley BP, Cook N, Richardson A, Barnett DB, Rosenthal FD. Circulating catecholamine, thyrotrophin, thyroid hormone and prolactin responses of normal subjects to acute cold exposure. *Clin. Endocrinol. (Oxf)* 1984; 21:285-91.
15. Ramoska E, Sacchetti AD. Propranolol-induced hypertension in treatment of cocaine intoxication. *Ann. Emerg. Med.* 1985; 14:1112-3.
16. Raven PB, Niki I, Dahms TE, Horvath SM. Compensatory cardiovascular responses during an environmental cold stress, 5°C. *J. Appl. Physiol.* 1970; 29:417-21.
17. Reed HL, Pepper S, Armstrong D, Von Tersch FJ, Lewis SB. Oxygen saturation of brachial venous blood correlates with fingertip temperatures between 11° and 39°C. *Aviat. Space Environ. Med.* 1989; 60:1068-71.
18. Scriven AJI, Brown MJ, Murphy MB, Dollery CT. Changes in blood pressure and plasma catecholamines caused by tyramine and cold exposure. *J. Cardiovasc. Pharmacol.* 1984; 6:954-60.
19. Tanaka S, Konno A, Hasimoto A, Hayase A, Takagi Y, Kondo S, Nakamura Y, Amura O. The influence of cold temperatures on the progression of hypertension: an epidemiological study. *J. Hypertens.* 1989; 7(Suppl 1):S49-S51.
20. Thuillez C, Richer C, Duhaze P, Bergougnan L, Giudicelli JF. β -Adrenoceptor blocking effects and plasma levels of bop-naprolol and propranolol in man. *Eur. J. Clin. Pharmacol.* 1985; 29:405-11.
21. Vuori I. The heart and the cold. *Ann. Clin. Res.* 1987; 19:156-62.
22. Wallin JD, Shah SV. β -adrenergic blocking agents in the treatment of hypertension: choices based on pharmacological properties and patient characteristics. *Arch. Intern. Med.* 1987; 147:654-9.

Accession For	
NTIS CRA&I	<input checked="" type="checkbox"/>
ERIC	<input type="checkbox"/>
US GPO	<input type="checkbox"/>
J. Clin. Mon.	<input type="checkbox"/>
By	
D. L. B. 11/1	
Availability Codes	
Dist	Avail. and/or Special
A-1	20